Regulatory Considerations for Zika Vaccines

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Zika virus in the Americas: an HHS expert consultation to accelerate the development of countermeasures
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Outline

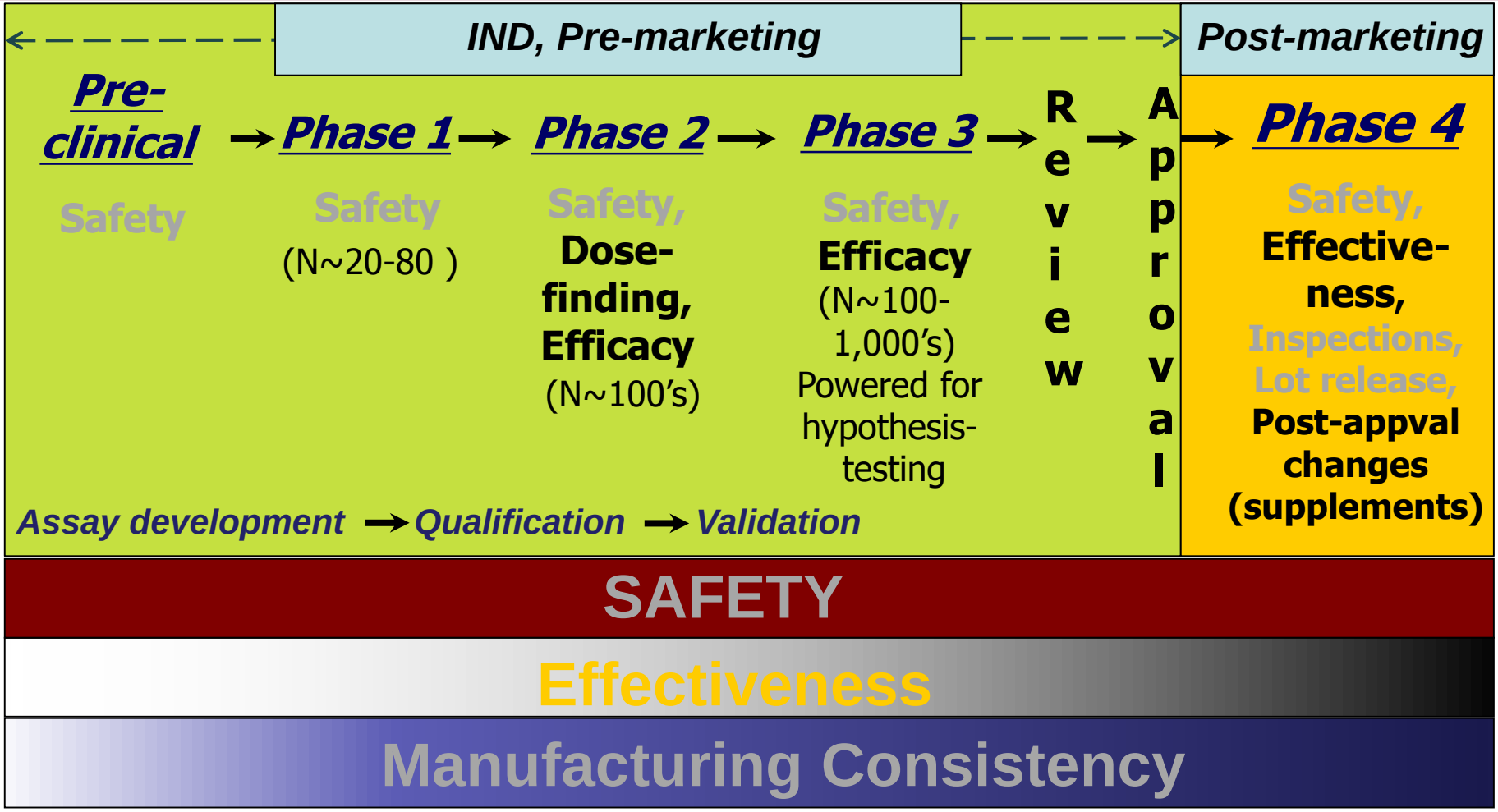
- Licensure of vaccines in the U.S.
- Lessons from other flavivirus vaccines
- Specific considerations in Zika vaccine development
- Summary and pathway forward

Biologics Licensure

Section 351 of the Public Health Service Act, 42 USC 262

- Must demonstrate
  - product is safe, pure and potent; and
  - facility in which the biologic product is manufactured, processed, packed, or held meets standards designed to assure that the biologic product continues to be safe, pure and potent; …
- Only those biologics that are demonstrated to be safe and effective, and that can be manufactured in a consistent manner will be licensed by the FDA

Development of Preventive Vaccines



Pathways for Licensure of Vaccines

- **“Traditional”**
- **Accelerated**
- **Animal Rule**

Demonstration of clinical safety required for all pathways

Approaches to demonstration of effectiveness differs among pathways

Safety Database Considerations

- Nature of the product
- Intended use
- Severity of the disease to be prevented
- Pre-clinical safety

Demonstrating Vaccine Effectiveness

"Traditional"- expectation of adequate and well-controlled clinical studies demonstrating:

- prevention of disease ***or***
- Immunologic response, in some cases
  - scientifically well-established immunologic marker to predict protection that can be reliably measured in a validated assay
  - facilitated by an understanding of disease pathogenesis and mechanism by which vaccine prevents disease

Demonstrating Vaccine Effectiveness (cont'd)

- **Accelerated** approval – for product addressing serious or life-threatening illnesses and provide meaningful therapeutic benefit over existing therapy; adequate and well-controlled clinical trial using ***surrogate*** endpoint reasonably likely to predict clinical benefit; need to ***verify*** clinical benefit post-approval (*21 CFR Subpart E, 601.41*)

- **Animal Rule** approval – for serious or life-threatening conditions; definitive human efficacy studies not ethical or feasible; efficacy based on adequate and well-controlled animal studies; need to ***verify*** clinical benefit during exigency (*21 CFR Subpart H, 601.90-95*)

Immune “Correlate” and Traditional Approval

- Scientifically well-established immunologic marker to predict protection that can be reliably measured in a validated assay

- Facilitated by an understanding of disease pathogenesis and mechanism by which vaccine prevents disease

U.S. Licensed Flavivirus Vaccines

- Yellow Fever, 17D live-attenuated – 1935, later YF-Vax 1978
  - protection first demonstrated in monkey challenge model
  - safety and immunogenicity evaluated first in immune then YF-naïve subjects
  - early field studies in Brazil
  - $\log_{10}$ neutralization index of ≥0.7 considered a threshold for protection based on monkey challenge
- Japanese Encephalitis, inactivated (JE-Vax) 1992, Ixiaro 2009
  - JE-Vax approval based on Thai efficacy trial in children 1-14 yo
  - Ixiaro approved based on immunogenicity ($PRNT_{50}$) non-inferiority to JE-Vax
  - $PRNT_{50}$ titer of 1:10 considered a threshold for protection based on mouse and human data.

Product development
"Begin with the end in mind"
- the Intended Use (Indication)

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

Zika Vaccines – Potential Target Populations

- **Endemic Areas**
  - **Children**
  - **Adolescents**
  - **Non-pregnant females of child-bearing age**
  - **Pregnant women and sexual partners**
  - **Others?**
- **Non-endemic Areas**
  - **Travelers to endemic areas**

Knowledge Gaps and Vaccine Development

- Acute Zika disease clinically resembles other co-existing arboviral diseases; definitive diagnosis requires RT-PCR during short window of low-level viremia
- Low titer of viremia suggests virus may be especially susceptible to neutralization. Can neutralizing antibody predict protection? (JEV or YF vs dengue)
- Retrospective diagnosis of Zika based on current serologic methods is difficult in those with pre-existing flaviviral antibodies due to extensive cross reactivity
- Role of NHP as infection vs disease model; other animal models?
- Duration of natural immunity and cross protection between Zika strains (serotypes?) and other flaviviruses to be defined
- Potential bi-directional modulation of Zika and dengue clinical disease, e.g. antibody-dependent enhancement (Zika < - > dengue) or cross-protection
- Incomplete characterization of risks of sequelae from infection, especially neurologic, e.g. microcephaly and Guillain-Barre syndrome

Clinical Considerations for Zika Vaccines in Pregnancy

- Unlike maternal immunizations designed to prevent neonatal or infant diseases (flu, RSV, pertussis, GBS), Zika vaccination during pregnancy is protection of the fetus *in utero*
- Major congenital malformations result from defective formation of the neural tube during the 3rd and 4th weeks
- Is sterile immunity necessary to prevent viral transmission to fetus? Protection against Zika viremia must be in place at the latest by the 3rd week, prior to neural tube formation
- Active transfer of IgG across the placenta differs by subclass and avidity. Maternal transfer of antibody very minimal before 6 weeks gestation.
- Protective neutralization antibody response typically takes 2 weeks, may be longer depending on vaccine type and regimen
- Safety and immunogenicity should be studied in pregnant females after their demonstration in non-pregnant adult females
- Need for vaccination of male partner to prevent sexual transmission during pregnancy

Dengue Vaccines in Humans 2016

- Live-attenuated (LAV)
  - Recombinant chimeras
  - Cell passaged
- Purified formalin-inactivated (PIV)
- Recombinant E-protein
- PrM/E Plasmid DNA
- Heterologous prime boost with LAV and PIV

VanniceK et al Vaccine 2016

Summary

- Vaccines are licensed based on determination of safety, purity and potency and consistency of manufacture.
- Three different approaches to demonstrating vaccine effectiveness for licensure
- Major gaps exist in knowledge in Zika virus epidemiology, diagnosis, virulence, transmission, protective immunity, interactions with other co-circulating arboviruses
- Prevention of disease due to Zika is the most direct way to demonstrating vaccine effectiveness; other approaches can be considered as knowledge accumulates
- Lessons can be drawn from experience with other successful flavivirus vaccines where licensure pathways are well-worked out
- Protecting pregnant women is a priority but demonstrating vaccine effectiveness in non-pregnant population is more direct
- Each vaccine is unique. Early discussion with FDA can expedite each specific vaccine's development.

Thank You!

U.S. FDA Office of Vaccine Research and Review

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